Regarding "Limitations in the use of rifampicin-gelatin grafts against virulent organisms"

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The rationale underlying planning treatment of major aortic graft infection (MAGI) is, at first sight, deceptively simple: eradication of infection, minimization of the operative risk, and prevention of recurrence. In the early 1990s, total graft excision (TGE) with in situ replacement with a rifampicin-bonded graft (ISRG) was introduced as a potential alternative to the "gold standard" of TGE with extraanatomic bypass.[1-5] ISRG offered the prospect of a shorter operation time, less physiologic stress to an already sick patient, and optimal pelvic and lower limb blood flow, and it avoided the risk of aortic stump blow-out and late amputation after thrombosis of axillofemoral grafts.[2-5] The principal worry, however, was whether short-term gain (reduced operative mortality and amputation rates) was to be exchanged for long-term pain (reinfection and its sequelae).

In fact, a review of the four largest series published to date suggests that the results of ISRG appear to be extremely good.[2-5] The operative mortality rate was 5%, the early and late amputation rate was 0%, and the reinfection rate was a gratifying 15%. However, these results may not be generalizable to routine clinical practice. First, only 40 patients were reported in these studies. Second, the largest experience by Bandyk et al[5] (16 patients) was highly selected and largely comprised patients with Staphylococcus epidermidis MAGI. It was also unclear as to the actual rate of reinfection in this series.[5] Third, many of the patients underwent treatment in the era before the widespread emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). In the updated Leicester series,[3] we observed that ISRG was probably unwise in patients with MRSA. Subsequently, a 1-year prospective audit by the Joint Vascular Research Group (JVRG), a collaboration of academic vascular research units, found that MRSA was now the predominant organism responsible for complex wound and graft infections in the United Kingdom and Ireland. Moreover, MRSA infections were associated with an extremely poor outcome, irrespective of location.[6] Even native artery and autologous vein was not immune.[6,7]

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Accordingly, publication of the paper by Koshiko and colleagues is timely because it specifically addresses the question of whether ISRG is effective in the presence of more virulent organisms, such as MRSA and *Escherichia coli*. Their data suggest that the gelatin sealant and antibacterial activity remained for about 2 weeks after implantation (actually more than was previously expected[8]). In vitro study results suggested that ISRGs were effective against *S epidermidis* infections for 2 to 3 weeks but retained sufficient antibacterial activity for only 48 hours against MRSA and *E coli*. Finally, in vivo animal study results appeared to corroborate the in vitro findings regarding the inability of ISRGs to protect against ongoing perigraft infection in the presence of MRSA and *E coli*. Their conclusion was that ISRG was a potential option for the treatment of *S epidermidis* infections but that it was "inapplicable" to use them in the presence of more virulent organisms.

At first sight, these seem to be rather damning data for the proponents of ISRG, particularly because autologous venous conduits (superficial femoral, greater saphenous) have emerged as alternative options for in situ revascularization.[9] However, even assuming that their conclusions regarding MRSA are correct (which I think they are), before abandoning the potential benefits of ISRG in other types of graft infection (shorter procedure in ill patients, no lower limb venous complications), a number of issues regarding the design of Koshiko et al's study must be considered.

First, the authors prepared their rifampicin solution 24 hours before graft irrigation. In normal clinical practice, the solution is prepared in theatre and immediately applied to the graft. The authors conceded that the antibacterial activity decreased with time at room temperature, but it would be interesting to know whether validation studies had been done on their 24-hour refrigerated samples. Second, a low concentration of rifampicin was used in this study (1 mg/mL). In almost every clinical series published to date, the concentration of rifampicin has been 60 mg/mL (600 mg rifampicin in 10 mL solvent), and this may be clinically important. Third, although it is accepted that the standard National Committee for Clinical Laboratory Standards method for gauging antibiotic activity requires the inoculation of 2 mL solution containing 1 to 2 □ 10^8 organisms directly onto the graft, it remains to be seen whether this truly reflects the natural history of the evolution of graft infection in clinical practice as opposed to the innoculum required to secure a graft infection. Intuitively, one believes that a spectrum of contamination is inevitably encountered in normal graft infection patients. Accordingly, the large bacterial load may reflect

an unlikely clinical scenario (with respect to direct contamination), and it cannot represent the typical volume of contamination in hematologically mediated graft infection. Fourth (and very importantly), none of the animals received any antibiotics, either prophylactically or therapeutically. It would certainly be our practice to treat suspected MAGI with systemic, broad-spectrum antibiotics until cultures and sensitivities were available, revise them thereafter, and continue treatment for at least 6 weeks. Finally, most exponents of TGE and ISRG would normally wrap the bonded graft with omentum to protect the prosthesis from potentially infected perigraft tissues. This was not done in any of the animals. In this respect, it is interesting to observe that no positive MRSA or *E coli* culture results were obtained directly from the ISRG grafts at death, whereas the perigraft tissues always had positive results. It is possible that omental wrapping may have given the host's immune response a chance to counter the perigraft infection, especially if antibiotics had also been administered.

In summary, this paper has rightly focused attention on the role of ISRG in MAGI. I think that almost every vascular surgeon would now be reluctant to consider ISRG as a first line option in patients with suspected MRSA aortic infection. However, the available clinical evidence[2-5] suggests that ISRG may still have an important role in the management of other types of infection, including some of the more virulent subtypes. This must be clarified before a potentially important treatment option is discarded. However, as was alluded to earlier, only 40 cases formed the basis of the clinical review for this commentary. Many more patients, worldwide, must have undergone treatment with ISRG, and it would be helpful to know of early and late outcomes with respect to the type of organism cultured at operation and the type of presentation (low-grade infection, enteric fistula, abscess, gross sepsis).

The one problem facing all of us is that we usually do not know what the responsible organism is until after the operation, despite preoperative and perioperative cultures and gram stains. It may be that only the "good results" after ISRG have been published to date. Those investigators with poorer outcomes should be encouraged to submit their data so as to make the evidence more generalizable. In an ideal world, the issue would be settled with a randomized trial. Members of the JVRG have considered this, but there were many logistic difficulties, not least the numbers needed for valid statistical analysis and the inevitable problems with inclusion and exclusion criteria. For many, the emergence of MRSA has already changed everything. The evidence from the JVRG audit was that once MRSA was identified as being responsible for the graft infection, treatment tended to be graft excision and amputation with the primary aim being preservation of life.[6] In situ reconstruction with autologous tissues may seem to be an attractive option, but the JVRG experience is that neither they nor native artery are a barrier to MRSA infection.[6,7] It remains to be seen whether the respective roles for ISRG, in situ revascularization with autologous vein, or TGE with extraanatomic bypass can be clarified before fear of MRSA dictates all management decisions.

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Please see the related article by Dr Susumu Koshiko et al on pages 779-85.